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(54) Title: COMBINED THERAPY AGAINST TUMORS COMPRISING ESTRAMUSTINE PHOSPHATE AND LHRH AGONISTS OR ANTAGONISTS

(57) Abstract: A method for treating tumors in a mammal, including humans, in need of such a treatment including administering simultaneously, separately or sequentially to said mammal estramustine phosphate and a LHRH agonist or antagonist, in amounts sufficient to achieve a therapeutically useful effect.

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COMBINED THERAPY AGAINST TUMORS COMPRISING ESTRAMUSTINE PHOSPHATE AND LHRH AGONISTS OR ANTAGONISTS

FIELD OF THE INVENTION

The present invention relates to the field of cancer treatment and provides a combination therapy for treating cancers in mammals, including humans, comprising the steps of administering estramustine phosphate and Luteinzing Hormone Releasing Hormone agonists or antagonists, hereinafter shortly referred to as LHRH agonists or antagonists, respectively.

BACKGROUND OF THE INVENTION

Estramustine phosphate is a known anti-mitotic agent currently used, in therapy, in the treatment of advanced adenocarcinoma of the prostate. For a general reference to estramustine phosphate, either as a single agent or in combination therapies against a variety of tumor types see, for instance, the international patent application WO 99/49869, which is herewith incorporated by reference.

LHRH agonists or antagonists are known therapeutic agents used in the treatment of hormone-dependent cancers such as, for instance, hormone-dependent breast and endometrial cancer. As an example, in U.S. Pat. No. 4,472,382 it is disclosed that prostatic adenocarcinoma, benign prostatic hypertrophy and hormone-dependent mammary tumors can be treated with various LHRH agonists and that prostate adenocarcinoma and benign hypertrophy can be treated by use of various LHRH agonists.

Some clinical improvement in pre-menopausal women with breast cancer by use of the two LHRH agonists, Buserelin and Leuprolide, is also reported by H. A. Harvey et al. "LH-RH analogs in the treatment of human breast cancer", LHRH and its Analogs – A new Class of contraceptive and therapeutic Agents (B. H. Vickery and J. J. Nestor, J., and E. S. E. Hafez, eds) Lancaster, MTP Press, (1984) and the J. G. M. Klijn et al., "Treatment with luteinizing hormone-relating hormone analogue (Buserelin) in premenopausal patients with metastatic breast cancer", Lancet 1, 1213-1216 (1982).

It is thus a first object of the present invention to provide a therapeutic method for treating tumors in a mammal in need of such a treatment, including humans, comprising administering simultaneously, separately or sequentially to said mammal estramustine phosphate, or a pharmaceutically acceptable salt thereof, and a LHRH agonist or antagonist, in amounts and close in time sufficient to achieve a therapeutic useful effect.

The present invention also provides the use of estramustine phosphate, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancers in a patient undergoing a simultaneous, separate or sequential treatment with a LHRH agonist or antagonist.

The invention also provides a product containing estramustine phosphate, or a pharmaceutically acceptable salt thereof, and a LHRH agonist or antagonist as a combined preparation for simultaneous, separate or sequential use in treating cancers.

Examples of such cancers are testicular cancer, prostate cancer, ovarian cancer, pancreatic cancer, uterine cancer, celomic epithelial carcinoma, germ cell ovarian cancer, fallopian tube ovarian cancer, breast cancer, lung cancer, colorectal cancer, brain cancers and melanoma. In one embodiment of the invention, such cancers are prostate cancer, ovarian cancer and breast cancer.

Examples of LHRH agonists according to the invention are, e.g., leuprorelin, deslorelin, triptorelin, buserelin, nafarelin, goserelin, avorelin, histerelin, compound PTL 03001 (5-oxo-L-propyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide) (Peptech), compound AN 207 (6-[N6-[5-[2-[1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-mehoxy-6,11-dioxo-4-[[2,3,6-trideoxy-3-(2,3-dihydro-1H-pyrrol-1-yl)α-L-lyxo-hexopyranosyl]oxy]-2-naphthacenyl]-1,5-dioxopentyl]-D-lysine]-,(2S-cis)-) (ASTA Medica Inc.), compound AN 238 L-threoninamide, N-[5-[2-[(2S,4S)-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-4-[[2,3,6-trideoxy-3-(2,3-dihydro-1H-pyrrl-1-yl)α-L-lyxo-hexopyranosyl]oxy]-2-naphthacenyl]-2-oxoethoxy]-1,5-dioxopentyl]-D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-, cyclic (2 7)-disulfide (ASTA Medica Inc.), compound AN 201, compound SPD 424 (LHRH-hydrogel implant) (Shire Pharmaceuticals Group) compound TX 397 (Theramex SAM), and danazol, or a pharmaceutically acceptable salt thereof. In one embodiment of the invention, LHRH agonists

are triptorelin and goserelin, or a pharmaceutically acceptable salt thereof, in particular triptorelin or a pharmaceutically acceptable salt thereof.

Examples of LHRH antagonists, according to the invention, are e.g. cetrorelix, abarelix, ramorelix, teverelix, ganirelix, compounds A 75998 (Acetyl-D-(2-naphthyl)alanyl-D-(4-chlorophenyl)alanyl-D-(3-pyridyl)alanyl-seryl-(N-methyl)tyrosyl-N6-(nicotinoyl)-D-lysyl-leucyl-N6-(isopropyl)lysyl-propyl-D-alaninamide) and A 84861 (Tetrahydrofuran-2-(S)-ylcarbonyl-glycyl-D-(2-naphthyl)alanyl-D-(4-cholro)phenylalanyl-D-(3-pyridyl)-alanyl-L-(N-methyl)tyrosyl-D-[N6-(3-pyridylcarbonyl)]lysyl-L-leucyl-L-(N6-isopropyl)lysyl-L-propyl-D-alanylamide) (Abbot Labs.), compound PM-OV-92 (Protherics), GnRH immunogen (Aphton Co.), compound D 26344 (ASTA Medica), compound T 98475 (Isopropyl 3-(*N*-benzyl-N-methylaminomethyl)-7-(2,6-difluorobenzyl)-4,7-dihydro-2-(4-isobutyrylaminophenyl)-4-oxothieno[2,3-*b*pyridine-5-carboxylate hydrochloride) (Takeda), and compound MI 1544 (Acetyl-D-tryptophyl-D-cyclopropyl-alanyl-D-tryptophyl-L-seryl-L-tyrosyl-D-lysyl-L-leucyl-L-arginyl-L-propyl-D-alaninamide), or a pharmaceutically acceptable salt thereof. In one embodiment, a LHRH antagonist is cetrorelix or a pharmaceutically acceptable salt thereof.

The inventors of the present invention have also found that treatment of the above-mentioned cancers by combined administration of a therapeutically effective amount of estramustine phosphate, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of a LHRH agonist or antagonist, can produce a therapeutic effect which is greater than that obtainable by single administration of a therapeutically effective amount of either sole estramustine phosphate or the sole LHRH agonist or antagonist. Namely, such combined therapy provides a synergistic or superadditive therapeutic effect, without being paralleled by toxic effects.

By the term "a superadditive or synergistic antitumor effect", as used herein, it is meant the inhibition of growth of a tumor, preferably the complete regression of the tumor, by administering a combination of estramustine phosphate and LHRH agonist or antagonist, to a mammal, including a human being, the result being advantageous compared to that obtained with the components of the combination when administered alone.

In one embodiment of the invention, the superadditive antitumor effect results in an anti-cancer therapy having increased effectiveness in controlling, i.e. slowing, interrupting,

arresting, stopping or reversing, the neoplasm formation.

As used herein, "controlling the growth" of the neoplasm refers to slowing, interrupting, arresting or stopping its growth and it does not indicate, necessarily, a total elimination of the neoplasm.

Therefore, the term "treating" simply means that life expectancy of an individual affected with a cancer will be increased, one or more of the symptoms of the disease will be reduced and/or quality of life will be enhanced.

Method and Administration

In effecting treatment of a patient in a therapy method according to the invention, the estramustine phosphate and the LHRH agonist or antagonist can be administered in any form or mode which makes the compounds bioavailable in effective amounts, including oral and parenteral routes.

By the term "administered" or "administering" as used herein is meant any acceptable manner of administering a drug to a patient which is medically acceptable including parenteral and oral administration.

By "parenteral" is meant intravenous, subcutaneous, intradermal or intramuscular administration. Oral administration includes administering one or both of the constituents of the combined preparation in a suitable oral form such as, e.g., tablets, capsules, suspensions, solutions, emulsions, powders, syrups and the like.

The actual method and order of administration of the combined preparations of the invention can vary according to, inter alia, the particular pharmaceutical formulation of the estramustine phosphate derivative being used, the particular pharmaceutical formulation of the LHRH agonist or antagonist being used, the particular cancer to be treated and the conditions of the patient being treated.

In the combined method of treatment according to the subject invention, the estramustine phosphate derivative can be administered simultaneously with the LHRH agonist or antagonist or the compounds can be administered sequentially, in either order.

Dosage

The dosage ranges for the administration of the combined preparation can vary with the age, condition and extent of the disease in the patient and can be determined by one of skill in the art.

The dosage regimen must therefore be tailored to the particular of the patient's conditions, response and associated treatments in a manner that is conventional for any therapy, and can be adjusted in response to changes in conditions and/or in light of other clinical conditions.

According to the invention, estramustine phosphate can be administered orally or parenterally, through a central or peripheral intravenous route. According to one embodiment, it is administered at dosages, per single intravenous infusion, exceeding 1300 mg or 950 mg/m^2. The solution intended for injection, for instance containing estramustine phosphate as meglunine salt, is then given as intravenous infusion with the preferred duration of infusion time varying from about 30 minutes to 3 hours.

When estramustine phosphate is administered through a peripheral intravenous route, a longer duration of infusion and greater total infusional volume can be utilized to minimize vascular irritation. The estramustine phosphate solution can also be mixed with various amounts of human albumin plasma proteins, cyclodextrins and amino acids, for instance arginine, so as to minimize any potential vascular damage.

Advantageously, estramustine phosphate can be intravenously administered together with arginine in different ratios, also including estramustine phosphate arginine salt.

When estramustine phosphate is administered through a central venous route, the administration can be performed through either a temporary or permanent venous access device, according to conventional methods.

Alternatively, estramustine phosphate can be orally administered, for instance as disodium salt, in the form of capsules or tablets. According to an alternative embodiment of the invention, estramustine phosphate disodium salt can be thus conveniently administered in solid

oral dosage forms also containing cyclodextrin and derivatives thereof. For a general reference to the administration of estramustine phosphate disodium salt and cyclodextrin see the International patent application WO 96/09072, in the name of Pharmacia AB, and herewith incorporated by reference.

An effective amount of LHRH agonist or antagonist is in general the one commonly used in therapy for such compounds. For instance, cetrorelix can be administered as single intramuscular administration of slow release cetrorelix 60 mg followed by a second injection after 24 hours then 60 mg every 3-4 weeks. Goserelin can be administered as goserelin acetate by subcutaneous administration of slow release goserelin at a dosage from about 3 to about 12 mg. Triptorelin can be administered for instance as triptorelin pamaote by intramuscular administration of long acting formulation, such as 1, 2, 3 or 4 months depot triptorelin formulation at a dosage from about 3 to about 20 mg. In particular triptorelin pamoate can be intramuscularly administered in the form of microparticles as described in US Pat. No. 5,225,205 and US Pat. No. 5,776,885, and more specifically as Trelstar® 1-month Depot formulation 3.75 mg.

Another embodiment of the invention comprises a method of treating a cancer selected from prostate, ovarian and breast cancer in a mammal in need of such treatment, comprising administering substantially simultaneously to said mammal estramustine phosphate and triptorelin or a pharmaceutically acceptable salt thereof, in amounts and close in time sufficient to achieve a therapeutically useful effect.

An additional embodiment of the invention provides the use of estramustine phosphate in the manufacture of a medicament for treating a cancer selected from prostate, ovarian and breast cancer in a mammal, undergoing a substantially simultaneous treatment with triptorelin or a pharmaceutically acceptable salt thereof.

As stated above, the invention also provides kits or single packages combining the pharmaceutical compositions useful for the combination treatment of the selected cancers discussed above. The kits or packages can also contain instructions to use the pharmaceutical compositions in accordance with the present invention.

A pharmaceutical composition for intramuscular administration containing triptorelin pamoate in the form of Treltar® Depot can be prepared as described in US Pat. No. 5,225,205 and US Pat. No. 5,776,885, herein incorporated by reference. A pharmaceutical composition for intravenous use comprising estramustine phosphate can be prepared as described in the aforementioned WO 99/49869.

As an additional example, estramustine phosphate arginine formulations can be prepared as follows:

Example 1

Preparation of estramustine phosphate arginine salt (estramustine phosphate:arginine=1:1 molar ratio) formulation for injection

300 mg of estramustine phosphate were weighed in a beaker and dispersed by means of magnetic stirring in 5 ml of water. 101 mg of arginine base were then added to the watery dispersion of the active whilst maintaining under stirring until a clear solution was obtained. The prepared solution was then brought to the final volume of 10 ml with water so as to reach a final concentration of 30 mg/ml of estramustine phosphate and 10.1 mg/ml of arginine (1:1 molar ratio respectively).

Example 2

Preparation of estramustine phosphate arginine salt in admixture with arginine (estramustine phosphate:arginine=1:2 molar ratio) formulation for injection

300 mg of estramustine phosphate were weighed in a beaker and dispersed by means of magnetic stirring in 5 ml of water. 202 mg of arginine base were then added to the watery dispersion of the active whilst maintaining under stirring until a clear solution was obtained. The basic pH of the obtained solution was brought to the physiological value of about 7.5 by slow addition of diluted hydrochloric acid.

The solution was then brought to the final volume of 10 ml with water so as to reach a final concentration of 30 mg/ml of estramustine phosphate and 20.2 mg/ml of arginine (1:2 molar ratio respectively).

CLAIMS

1. A method for treating tumors in a mammal, including humans, in need of such a treatment comprising administering simultaneously, separately or sequentially to said mammal estramustine phosphate, or a pharmaceutically acceptable salt thereof, and a LHRH agonist or antagonist, in amounts sufficient to achieve a therapeutically useful effect.

2. A method according to claim 1, wherein the mammal is a human

3. A method according to claim 1, wherein the tumor is selected from the group consisting of testicular cancer, prostate cancer, ovarian cancer, pancreatic cancer, uterine cancer, celomic epithelial carcinoma, germ cell ovarian cancer, fallopian tube ovarian cancer, breast cancer, lung cancer, colorectal cancer, brain cancers and melanoma.

4. A method according to claim 3, wherein the tumor is selected from the group consisting of prostate, ovarian and breast cancer.

5. A method according to claim 1, wherein the LHRH agonist is selected from the group consisting of leuprorelin, deslorelin, triptorelin, buserelin, nafarelin, goserelin, avorelin, histerelin, compound PTL 03001 (5-oxo-L-propyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide), compound AN 207 (6-[N6-[5-[2-[1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-mehoxy-6,11-dioxo-4-[[2,3,6-trideoxy-3-(2,3-dihydro-1H-pyrrol-1-yl)α-L-lyxo-hexopyranosyl]oxy]-2-naphthacenyl]-1,5-dioxopentyl]-D-lysine]-,(2S-cis)-), compound AN 238 L-threoninamide, N-[5-[2-[(2S,4S)-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-4-[[2,3,6-trideoxy-3-(2,3-dihydro-1H-pyrrl-1-yl)α-L-lyxo-hexopyranosyl]oxy]-2-naphthacenyl]-2-oxoethoxy]-1,5-dioxopentyl]-D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-, cyclic (2 7)-disulfide, compound AN 201, compound SPD 424 (LHRH-hydrogel implant), compound TX 397 (Theramex SAM), danazol, and a pharmaceutically acceptable salt thereof.

6. A method according to claim 5, wherein the LHRH agonist is selected from the group consisting of triptorelin, goserelin and the pharmaceutically acceptable salts thereof.

7. A method according to claim 1, wherein the LHRH antagonist is selected from the group consisting of cetrorelix, abarelix, ramorelix, teverelix, ganirelix, compound A 75998 (Acetyl-D-(2-naphthyl)alanyl-D-(4-chlorophenyl)alanyl-D-(3-pyridyl)alanyl-seryl-(N-methyl)tyrosyl-N6-(nicotinoyl)-D-lysyl-leucyl-N6-(isopropyl)lysyl-propyl-D-alaninamide), A 84861 (Tetrahydrofuran-2-(S)-ylcarbonyl-glycyl-D-(2-naphthyl)alanyl-D-(4-cholro)phenylalanyl-D-(3-pyridyl)-alanyl-L-(N-methyl)tyrosyl-D-[N6-(3-pyridylcarbonyl)]lysyl-L-leucyl-L-(N6-isopropyl)lysyl-L-propyl-D-alanylamide), compound PM-OV-92 (Protherics), GnRH immunogen, compound D 26344 (ASTA Medica), compound T 98475 (Isopropyl 3-(N-benzyl-N-methylaminomethyl)-7-(2,6-difluorobenzyl)-4,7-dihydro-2-(4-isobutyrylaminophenyl)-4-oxothieno[2,3-*b*pyridine-5-carboxylate hydrochloride), compound MI 1544 (Acetyl-D-tryptophyl-D-cyclopropyl-alanyl-D-tryptophyl-L-seryl-L-tyrosyl-D-lysyl-L-leucyl-L-arginyl-L-propyl-D-alaninamide), and a pharmaceutically acceptable salt thereof.

8. A method according to claim 7, wherein the LHRH antagonist is cetrorelix or pharmaceutically acceptable salts thereof.

9. A method according to claim 1, wherein estramustine phosphate, or a pharmaceutically acceptable salt thereof, is administered intravenously.

10. A method according to claim 9, wherein estramustine phosphate is administered intravenously at dosages, per single infusion, exceeding 1300 mg or 950 mg/m^2.

11. A method according to claim 9, wherein estramustine phosphate is administered intravenously as estramustine phosphate arginine salt or as estramustine phosphate meglumine salt with arginine.

12. A method according to claim 1, wherein estramustine phosphate, or a pharmaceutically acceptable salt thereof, is administered orally.

13. A method according to claim 1, wherein estramustine phosphate is in the form of estrmustine phosphate disodium salt.

14. Use of estramustine phosphate, or of a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a cancer selected from the group consisting of testicular cancer, prostate cancer, ovarian cancer, pancreatic cancer, uterine cancer, celomic epithelial carcinoma, germ cell ovarian cancer, fallopian tube ovarian cancer, breast cancer, lung cancer, colorectal cancer, brain cancers and melanoma, in a mammal undergoing a substantially simultaneous treatment with a LHRH agonist or antagonist.

15. Use according to claim 14, wherein the mammal is a human.

16. Use according to claim 14, wherein the LHRH agonist or antagonist is triptorelin.

17. Use according to claim 14, wherein the cancer is selected from the group consisting of prostate, ovarian and breast cancer.

18. Products comprising estramustine phosphate, or a pharmaceutically acceptable salt thereof, and a LHRH agonist or antagonist, as a combined preparation for simultaneous, separate or sequential use in the treatment of tumors.

19. Products comprising estramustine phosphate, or a pharmaceutically acceptable salt thereof, and triptorelin, as a combined preparation for simultaneous, separate or sequential use in the treatment of tumors.

20. Products according to claim 17, wherein the tumors are selected from the group consisting of testicular cancer, prostate cancer, ovarian cancer, pancreatic cancer, uterine cancer, celomic epithelial carcinoma, germ cell ovarian cancer, fallopian tube ovarian cancer, breast cancer, lung cancer, colorectal cancer, brain cancers and melanoma.